IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A09-03

Update search on report A05-19A (Cholinesterase inhibitors in Alzheimer's disease)[1]

Executive Summary

[1] Translation of the executive summary of the rapid report "Aktualisierungsrecherche zum Bericht A05-19A (Cholinesterasehemmer bei Alzheimer Demenz)" (Version 1.0; Status: 12.10.2009). Please note that this translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Update search on report A05-19A (Cholinesterase inhibitors in Alzheimer's disease)

Contracting agency:
Federal Joint Committee

Commission awarded on:
20.08.2009

Internal Commission No.:
A09-03

Publisher's address:
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Research question

In February 2007 the Institute for Quality and Efficiency in Health Care (IQWiG) produced a final report on "Cholinesterase inhibitors in Alzheimer's disease" (commission A05-19A). This final report represented the first in the series on the topic of "Alzheimer's disease". When the fourth and last assessment (commission A05-19C: "Memantine in Alzheimer's disease") was completed, the literature search for the final report A05-19A was already 3 years old. The Federal Joint Committee (G-BA) therefore commissioned IQWiG to determine whether substantive new evidence on cholinesterase inhibitors had been published since then that could decisively change the conclusions of that report so that a new assessment of cholinesterase inhibitors would be desirable.

Methods

The methods applied in producing this rapid report were first described in a project outline (version 1.0 dated 3 September 2009). The criteria for selecting studies corresponded to those of the final report A05-19A, supplemented by the inclusion of studies on rivastigmine as a transdermal therapeutic system (TTS), as this drug was only approved after publication of the final report A05-19A. Randomized controlled trials on cholinesterase inhibitors (compared with placebo, another anti-dementia treatment or compared with each other) with a duration of at least 16 weeks were included. In accordance with the approval status, only trials with patients having mild to moderate Alzheimer's disease were included.

A systematic literature search to identify studies was carried out in the following bibliographic databases: MEDLINE, EMBASE and in The Cochrane Library. In addition, literature indexes of relevant secondary publications, study registries and publicly accessible approval documents were searched. All sources were searched in September 2009. The literature screening was carried out by 2 reviewers independently of each other.

The ratio between the newly identified data and those already identified in the final report A05-19A was described according to each outcome. In addition, the effects (if provided in the publications) observed in the newly identified studies were compared to those in the final report A05-19A. Using this comparison, it was judged whether the statement on each outcome in the conclusion of the final report A05-19A seemed robust when taking the new data into account.

Based on the information on all outcomes, a reasoned presentation was then given as to whether an update to the final report A05-19A appeared worthwhile. It was possible that the

recommendation varied for individual parts of the assessment (e.g. recommendation for updating only 1 out of 3 drugs or only for a specific dose).

Results

Overall, 9 relevant studies were identified, 2 of which were through the bibliographic literature search. For all 7 additional studies identified in the study registries, no full publications were indicated. However, study synopses containing comprehensive data were referred to for 2 of these studies. Overall, sufficient information was available for 4 out of 9 identified studies to compare the results with those of the final report A05-19A. The 9 studies were divided between the individual therapy comparisons as follows (one of the studies investigated several relevant therapy comparisons):

- donepezil vs. placebo: 2 studies (both unpublished, but 1 study with study synopsis)
- galantamine vs. placebo: 3 studies (all unpublished, but 1 study with study synopsis)
- rivastigmine (p.o.[2]) vs. placebo: 1 study (published)
- galantamine vs. donepezil: 1 study (published)
- rivastigmine (TTS[3]) vs. placebo: 2 studies (1 published, 1 unpublished)
- rivastigmine (TTS) vs. rivastigmine (p.o.): 2 studies (1 published, 1 unpublished)

Donepezil vs. placebo

The inclusion of the results of the study with study synopsis (REFLECT-1) did not alter the conclusions of the final report A05-19A. Due to the low number of patients in the one unpublished study compared to the amount of data in the final report A05-19A and taking into account the effects determined in the final report A05-19A and confirmed by the REFLECT-1 study, it appears unlikely that the inclusion of the unpublished study would alter the quality of the results of the final report A05-19A.

In summary, there was no indication that a fresh assessment of the comparison between donepezil and placebo would alter the pertinent conclusions found in the final report A05-19A.

Galantamine vs. placebo

Of the 3 identified studies on the comparison between galantamine and placebo, analysable results in the form of a study synopsis were only available for 1 study (3301). Approximately

[2] peroral administration
[3] transdermal therapeutic system

400 patients were included in this study. There were no results available in another study with just over 1000 patients. A conference abstract was available for the third study, but its reporting of results was relatively limited. This third study is of particular importance as it includes an observation period of 2 years. In view of the comparatively large quantity of data without available results, a comparison of the results from study 3301 with those of the final report A05-19A was dispensed with. Overall, it appears possible that a fresh assessment of the comparison of galantamine vs. placebo would alter the pertinent conclusions found in final report A05-19A.

Rivastigmine (p.o.) vs. placebo

The inclusion of the results of the published IDEAL study on the research question of rivastigmine (p.o.) vs. placebo did not alter the conclusions of the final report A05-19A. Thus, there was no indication that a fresh assessment of the comparison of rivastigmine (p.o) vs. placebo would alter the pertinent conclusions found in the final report A05-19A.

Galantamine vs. donepezil

The inclusion of the results of the published Hong 2006 study on the research question galantamine vs. donepezil did not alter the conclusions of the final report A05-19A. Thus, there was no indication that a fresh assessment of the comparison of galantamine vs. donepezil would alter the pertinent conclusions found in the final report A05-19A.

Rivastigmine (TTS) vs. placebo and vs. rivastigmine (p.o.)

In addition to the published IDEAL study, 2 more unpublished studies on rivastigmine (TTS) were identified. These studies included a total of approximately 1000 patients, whereas the IDEAL study included a total of approximately 900 patients receiving approval-compliant treatment. As this provides additional unpublished data in relevant quantities in addition to the IDEAL study, it is not advisable to base an assessment of the rivastigmine patch solely on the IDEAL study.

In summary, the assessment of the new transdermal application of rivastigmine involves a new research question, which was not dealt with in the final report. If this research question was dealt with, it would lead to new conclusions compared to the conclusions found in the final report A05-19A.

Conclusions

For the comparisons of donepezil vs. placebo and rivastigmine (p.o.) vs. placebo there is no indication that a fresh assessment of these research questions would alter the pertinent conclusions found in the final report A05-19A. For the direct comparisons between the 3 cholinesterase inhibitors, donepezil, galantamine and rivastigmine, there is also no indication

that a fresh assessment of these research questions would alter the pertinent conclusions found in the final report A05-19A.

However, due to a relevant quantity of unpublished data in the comparison of galantamine vs. placebo, it appears possible in this case that a fresh assessment would alter the pertinent conclusions found in the final report A05-19A.

After the final report A05-19A was published, a new type of rivastigmine application was approved (patch for transdermal application). As a result, this type of application was not assessed in the final report A05-19A. Thus, if this research question was dealt with, it would lead to new conclusions compared to those found in the final report A05-19A.

Keywords: cholinesterase inhibitors, donepezil, galantamine, rivastigmine, Alzheimer's disease, systematic review

The full report (in German) is available on www.iqwig.de/index.905.html